ABSTRACT

We examined the effect of HLA class I haplotypes on HIV-1 seroconversion and disease progression in the Pumwani sex worker cohort. This study included 595 HIV-1 positive patients and 176 HIV negative individuals. HLA-A, -B, and -C were typed to 4-digit resolution using sequence-based typing method. HLA class I haplotype frequencies were estimated using PyPop 32-0.6.0. The influence of haplotypes on time to seroconversion and CD4+ T cell decline to <200 cells/mm3 were analyzed by Kaplan-Meier analysis using SPSS 13.0. Before corrections for multiple comparisons, three 2-loci haplotypes were significantly associated with faster seroconversion, including A*23:01-C*02:02 (p=0.014, log rank(LR)=6.06, false-discovery rate (FDR)=0.056), B*42:01-C*17:01 (p=0.01, LR=6.60, FDR=0.08) and B*07:02-C*07:02 (p=0.013, LR=6.14, FDR=0.069). Two A*74:01 containing haplotypes, A*74:01-B*15:03 (p=0.047, LR=3.942, FDR=0.068) and A*74:01-B*15:03-C*02:02 (p=0.045, LR=4.01, FDR=0.072) and B*14:02-C*08:02 (p=0.021, LR=5.36, FDR=0.056) were associated with slower disease progression. Five haplotypes, including A*30:02-B*45:01 (p=0.0008, LR=11.183, FDR=0.013), A*30:02-C*16:01 (p=0.015, LR=5.97, FDR=0.048), B*53:01-C*04:01 (p=0.010, LR=6.61, FDR=0.08), B*15:10-C*03:04 (p=0.031, LR=4.65, FDR=0.062), and B*58:01-C*03:02 (p=0.037, LR=4.35, FDR=0.066) were associated with faster progression to AIDS. After FDR corrections, only the associations of A*30:02-B*45:01 and A*30:02-C*16:01 with faster disease progression remained significant. Cox regression and deconstructed Kaplan-Meier survival analysis showed that the associations of haplotypes of A*23:01-C*02:02, B*07:02-C*07:02, A*74:01-B*15:03, A*74:01-B*15:03-C*02:02, B*14:02-C*08:02 and B*58:01-C*03:02 with differential seroconversion or disease progression are due to the dominant effect of a single allele within the haplotypes. The true haplotype effect was observed with A*30:02-B*45:01, A*30:02-C*16:02, B*53:01-C*04:01 B*15:10-C*03:04, and B*42:01-C*17:01. In these cases, the presence of both alleles accelerated the disease progression or seroconversion than any of the single allele within the haplotypes. Our study showed that the true effects of HLA class I haplotypes on HIV seroconversion and disease progression exist and the associations of HLA class I haplotype can also be due to the dominant effect of a single allele within the haplotype.